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Cardiovascular Disease Risk Assessment and Treatment of Erectile Dysfunction in Men with Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration between all authors. Author PCO designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors BN and JN managed the literature searches while authors DVE, ON and RO took care of the analyses of the materials. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Erectile dysfunction (ED) is the persistent inability to attain /or maintain an erection of the penis adequate for satisfactory sexual intercourse. This condition has been found to be more common, to occur earlier and to be more difficult to treat in men with Diabetes mellitus (DM) than those without DM. However, recent developments have led to improvement in the treatment of this condition with attendant reduction in associated psychosocial problems. This review article discusses the various treatment strategies for ED in men with DM, brings to fore the need for prior assessment of cardiovascular status of such patients before commencement of treatment for ED as well as the need for adequate glycaemic control and treatment of other co-morbidities in these patients.

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1. INTRODUCTION

The global prevalence of diabetes mellitus [DM] has been on a steady increase in the past 13 years, with 171 million people and 285 million people having the condition in the year 2000 and 2010 respectively and with a projection that this will increase to 439 million by the year 2030 [1,2]. The rising prevalence of DM comes with an increase in the morbidity and mortality associated with the condition which in turn results from the associated complications including erectile dysfunction [ED]. This makes DM a costly condition to manage [3].

Erectile dysfunction has been found to be 2-3 times more common in men with DM than in men without DM and is more severe and more resistant to treatment in DM patients [4]. While the prevalence of ED has been shown to increase progressively with age, it has been observed that ED occurs earlier in people with DM than in those without DM with more than 50% of men developing ED within 10 years of onset of DM [5].

Erectile dysfunction in DM arises as a consequence of multiple factors, mostly in combination, including vascular, neurological, hormonal, psychological abnormalities and drug treatment of co-morbid conditions like hypertension [6] whereas the consequences include depression, marital disharmony and low self esteem. Thus ED negatively affects the quality of life when it occurs in men with DM [7] making early diagnosis and appropriate treatment highly imperative. However, the good news is that these psychological consequences often improve with treatment of ED. This was demonstrated by Bocchio et al. [8] in their study in which they observed that obsessive compulsion, depression, anxiety and psychotic disorders in men with ED were all significantly improved after treatment with Tadalafil.

Treatment of ED in men with DM is multimodal and generally similar to treatment of ED in non diabetic men, however treatment of underlying hyperglycaemia and co-morbidities is paramount to prevent or halt the progression of the condition. These co-morbidities include hypertension, dyslipidaemia, obesity, smoking, sedentary lifestyle and depression [9,10]. It is also of utmost importance to choose drugs like antihypertensive agents and antidepressants with least impact on erectile function for treatment of co-morbidities in men with diabetes and ED [11]. While it is advised that antihypertensive drugs like alpha methyldopa, thiazide diuretics and non-selective beta-blocker as well as tricyclic antidepressants be avoided as much as possible, use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers is encouraged as these groups of drugs have the additional advantage of delaying onset and progression of microalbuminuria in diabetic patients [12-14].

Studies have shown that higher levels of glycated haemoglobin, which is a marker of poor glycaemic control, in men with DM is associated with ED, thus there is need for adequate glycaemic control in these men [15].

2. CARDIOVASCULAR DISEASE RISK ASSESSMENT IN MEN WITH DIABETES MELLITUS AND ERECTILE DYSFUNCTION

Before commencing treatment for ED, the cardiovascular status of diabetic men with ED should be assessed. Those with high cardiovascular disease [CVD] risk should not receive treatment for ED until their cardiac condition stabilizes or decision by Cardiologist or Internist that sexual activity can be safely resumed. These high CVD risk patients include those with severe/unstable angina, uncontrolled hypertension, systolic BP >180mmHg, New York Heart Association (NYHA) classes III and IV congestive heart failure, recent myocardial infarction or cerebrovascular accident, high risk arrhythmias, hypertrophic obstructive cardiomyopathy and moderate to severe valve diseases.Those with intermediate CVD risk should be evaluated by a Cardiologist before commencing treatment for ED while those with low CVD risk can be considered for first line treatment of ED. The Princeton 111 consensus on management of ED and CVD also emphasized the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with physical demands of sexual activity before prescribing treatment for ED [16].

Cardiovascular disease risk assessment and stratification in male diabetic patients with ED can be done using the Framingham risk score which estimates 10 year risk for myocardial

infarction or coronary death using age, sex, total cholesterol, high density lipoprotein cholesterol, smoking, systolic blood pressure and use of antihypertensive medications [17].

This cardiovascular risk assessment prior to treatment of ED is of paramount importance because various studies have shown that ED is an independent marker of CVD [18] and that ED frequently precedes coronary artery disease, peripheral artery disease, stroke and major cardiovascular events [19]. A detailed history and physical examination is also important as some patients with ED may have risk factors more than that estimated by Framingham risk score. Emphasis should be on measures of visceral adiposity, severity and duration of ED, presence of metabolic syndrome and obstructive sleep apnea as these have been shown to worsen overall CVD risk status [20-21].

Some patients with intermediate cardiovascular disease risk status may not have overt CVD and thus further evaluation with procedures like exercise stress testing, carotid intimal thickness, ankle brachial index and coronary artery calcium scoring has been recommended [19]. Some emerging prognostic markers have also been found useful in predicting CVD risk in men with ED and include carotid – femoral pulse – wave – velocity [22], serum testosterone, albuminuria and high sensitivity C – reactive protein. Serum testosterone levels < 8 nmol/L (230 ng/dl) in men with ED have been found to be associated with a significant increase in fatal major adverse cardiovascular events [23]. Similarly, increased mean urinary albumin – creatinine ratio $\geq$ 25 mg/mol was associated with a significantly increased risk of new cardiovascular events [24].

3. TREATMENT OF ERECTILE DYSFUNCTION IN MEN WITH DIABETES MELLITUS

The modalities for treatment of ED in men with DM can be grouped into first, second and third line. The first line treatment modalities include use of phosphodiesterase type 5 [PDE 5] inhibitors and vacuum erection devices while the second line modalities consist of intra-urethral suppository, intra-corporal injections and testosterone replacement therapy. The third line treatment modalities are basically surgical interventions. Newer methods like use of neurotrophic factors and nitric oxide synthase [NOS] aim at treating the underlying mechanisms of ED [11]. Other new modalities being studied for treatment of ED are soluble guanylate cyclase (sGC) stimulators / activators, Rho – kinase inhibitors, intracavernosal sodium nitrate donors and low intensity extracorporal shock wave therapy.

4. PHOSPHODIESTERASE 5 INHIBITORS

Phosphodiesterase 5 inhibitors have been described as the mainstay of oral medical treatment of ED in diabetic patients and include Sildenafil, Vardenafil and Tadalafil [11]. This group of drugs acts by inhibiting the action of PDE -5, the predominant phosphodiesterase in the smooth muscles of the penis. This prevents the degradation of cyclic Guanosine monophosphate (cGMP) leading to accumulation of cGMP which in turn leads to relaxation of arterial and trabecular smooth muscles. All these result in arterial dilatation, constriction of veins, and engorgement of the venous sinusoids with erection of the penis. El-Sarka et al. [25] observed that the global efficacy and overall patients' satisfaction were high among diabetic men treated with Sildenafil for ED but the efficacy of the drug was negatively affected by factors like poor glycaemic control, longer duration of DM and presence of more than one DM related complications. Similarly Rendel et al. [26] in a randomized clinical trial involving 268 diabetic men with ED, observed that 56% of those on Sildenafil compared to 10% of those on placebo had improved erections while 61% of those on Sildenafil and 22% of those on placebo had successful attempts respectively at sexual intercourse. Vardenafil and Tardalafil have been equally found to cause significant improvement in erectile function and frequency of successful sexual intercourse [27,28].

5. VACUUM ERECTION DEVICE

Vacuum erection device consists of a cylindrical chamber with an opening at one end and a pumping mechanism at the other end which can either use battery or be manually operated. The base of the penis is lubricated and the pump is then placed over the penis creating a tight seal against the base of the penis. When the pump is activated, it creates a negative pressure of about 200 – 250 mmHg within the pump which causes blood to fill the corporal bodies of the penis. After penile engorgement, a tension ring is placed at the base of the penis to trap the blood in the corporal bodies after which the pump is removed and erection is maintained. It must however be emphasized that the constriction ring should not

remain in place for more than 30 minutes. More than 70% of diabetic men with ED using vacuum erection device were able to achieve satisfactory erections but about 30% of them had to discontinue its use because of inadequate rigidity, penile pain, failure to ejaculate and appearance of the penis while using the device [29,30].

6. INTRAURETHRAL SUPPOSITORIES AND INJECTIONS

Intraurethral Alprostadil suppository as well as intracavenosal injection of agents like Papaverine, Phentolamine and Prostaglandin E_1 [PGE_1] can also be used to treat ED in diabetic men and have been shown to significantly increase the frequency of satisfactory erections and successful sexual intercourse [31- 33].

7. PENILE PROSTHESIS

When pharmacological therapy fails or is contraindicated and/or patients do not tolerate vacuum devices, penile prosthesis [implants] can be used and overall satisfaction with penile prosthesis has been found to range from 69 to 81%. However, diabetic patients may have increased risk of penile prosthesis associated infection than non diabetic men [11,34,35].

8. TESTOSTERONE REPLACEMENT THERAPY

Testosterone replacement has also been found to be beneficial in the treatment of ED in men with DM as it not only improves erectile function but also improves efficacy of PDE-5 inhibitors [36-38]. This effect was noticed to be more demonstrable in patients with hypogonadism. In the multicentre, placebo-controlled TAD TEST study, 178 men with ED who did not respond to 10mg once daily dose of Tadalafil for 4 weeks were divided into 2 and one group was additionally given placebo while the other group additionally received 0.1% Testosterone gel for 12 weeks. It was observed that among patients that received additional Testosterone replacement therapy, those with Testosterone levels ≤300 ng/dl (10.4 nMol/L) had significant improvement in sexual function compared to those that received placebo. On the other hand, there was no additional effect noticed among patients with Testosterone levels of 337±14.8 ng/dL (11.7±0.5 nmol/L) who received Tadalafil plus Testosterone gel [39].

Testosterone can be given by injection, patch, topical gel, pill or implant. Associated side effects include hepatotoxicity and polycythaemia, with frequency of occurrence varying with route of administration. Intramuscular preparations have been shown to improve International Index of Erectile Function (IIEF) scores better than gel [40,41].

9. NEW AND EMERGING TREATMENT MODALITIES FOR ERECTILE DYSFUNCTION

In an attempt to develop treatment modalities that will take care of the underlying pathophysiologic mechanism of ED and those that will have longer lasting effects, new treatment approaches are being continually developed. These include soluble guanylate cyclase (sGC) stimulators / activators, Rho – kinase inhibitors, intracavernosal sodium nitrate donors and low intensity extracorporal shock wave therapy which are discussed below.

10. LOW INTENSITY EXTRACORPOREAL SHOCK WAVE THERAPY

This treatment modality uses low intensity shock waves directed at the corpora carvenosa to induce mechanical stress and micro trauma which in turn stimulate release of angiogenic factors and subsequent neovascularization of the treated tissues with improvement in blood supply. This is believed to be able to restore the erectile mechanisms, thus enabling natural and spontaneous erections. It has been shown to offer significant clinical improvement of erectile function and penile haemodynamics without any adverse effect [42] and is expected to be of immense benefit to diabetic men with ED as this is significantly of vascular origin.

11. SOLUBLE GUANYLATE CYCLASE STIMULATORS/ACTIVATORS

Cyclic GMP is important in the production of penile erection in men as it facilitates the relaxation of the trabecular smooth muscles of the penis. Its formation from guanosine triphosphate (GTP) is facilitated by the receptor sGC. This conversion of GTP to cGMP is also increased by the binding of nitric oxide (NO) to sGC. However, while the production of NO may be impaired in some individuals, it has been shown that endogenous NO released from nitrergic nerves in the corpora cavernosa is significantly reduced in diabetes and

hypertension leading to decreased activation of the NO – sGC – cGMP pathway and this may explain why some men with ED do not respond to PDE – 5 inhibitors. In an attempt to circumvent this problem, agents that can act directly on sGC, independent of NO, were developed and these are called sGC stimulators and activators. These drugs have shown some promise in the treatment of ED [43].

12. RHO KINASE INHIBITORS

Rho kinase has been shown to contribute to smooth muscle tone in corpus carvenosum by inhibiting the regulatory subunit of myosin light chain phosphatase [44]. Thus when inhibitors of Rho kinase were injected into the carvenous sinuses, a resultant increase in the intracarvenosal pressure was noticed within minutes, without significantly reducing the systemic blood pressure. The Rho kinase inhibitor Fasudil has been shown to be effective in treatment of ED in diabetic rats [45], raising hope for future use in humans.

13. INTRACAVERNOSAL SODIUM NITRATE DONORS

Nitric oxide is a potent vasodilator involved in erectile function and reduction in its level or action has been implicated in the pathogenesis of ED. Thus increasing the availability of NO by intracavernosal injection of substances that increase the quantity of NO available to the vascular endothelium has been found to improve erectile function. Such substances include sodium nitrite and sodium nitroprusside [46].

14. CONCLUSION

Erectile dysfunction has been shown to occur more, occur earlier, and be more severe and more difficult to treat in men with DM than in those without DM. The methods of treatment of ED are generally similar among men with DM and those without DM and the recent developments in treatment modalities have led to improvement in sexual function among men with DM and ED with attendant reduction in the psychosocial consequences. However, there is need for adequate CVD risk assessment before commencement of treatment of ED in men with DM.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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